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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/749,962	GOVARDHAN ET AL.	
	Examiner	Art Unit	
	ALEXANDER KIM	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 February 2011*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *4,7-10,17,19-22,63-68,72-76 and 80* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4, 7-10, 17, 19-22, 63-68, 72-76, and 80* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *02/17/2011*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Application Status

1. In response to the previous Office action, a non-Final rejection (mailed on 08/24/2010), Applicants filed a response and amendment received on 02/09/2011. In said amendment, claims 1-3, 5-6, 11-16, 18, 23-62, 69-71, 77-79, and 81-84 are cancelled; claims 4, 7-9, 17, 19-21, 63-68, 72-76, and 80 are amended.

Claims 4, 7-10, 17, 19-22, 63-68, 72-76, and 80 are pending in the instant Office action and will be examined herein.

Information Disclosure Statement

2. The information disclosure statement (IDS) submitted on 02/17/2011 with a fee was filed after the mailing date of the first Office action on the merits on 08/24/2010. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner. A copy of Form PTO/SB/08 is attached to the instant Office action.

Withdrawn-Claim Objections

3. The previous objection of Claims 4, 7, 8 and 9 (Claims 10, 17-22 and 60-84 dependent therefrom) for reciting "A polyarginine containing crystal of human growth hormone (hGH)..." is withdrawn by virtue of applicants' amendment.

4. The previous objection of Claim 7 (Claims 10, 17-19, 22 and 60-63, 68-72, 76-80, 84 dependent therefrom) for reciting "$T^{90\%}$" is withdrawn by virtue of applicants' amendment.

5. The previous objection of Claim 17 (Claims 18-22 dependent therefrom) 22 under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim; for reciting "and an excipient" is withdrawn by virtue of applicants' amendment.

6. The previous objection of Claims 17-22 under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim is withdrawn by virtue of applicants' amendment.

Claim Objections

7. Claims 4, 7-10, 17, 19-22, 63-68, 72-76, and 80 are objected to because of the following informalities:

(a) Claim 17 (Claims 19, 21-22 dependent therefrom) recite "The composition according to claim 4, 7, 8, or 9". However, claims 1 and 7-9 are drawn to "A crystal of human growth hormone. Thus, claim 17 should recite ---The crystal of human growth hormone" or claims 4 and 7-9 should recite ---A composition...---, for example, to improve the format of claims. Similar change(s) are suggested in

claims 63 and 80 dependent therefrom. Similar change(s) are suggested in claims 74-76.

(b) Claims 19-21 recite "a polymer", "a polyamino acid, and/or "polyarginine" accompanied by "additional excipient". The said limitations above (i.e., "a polymer", "a polyamino acid, and/or "polyarginine") in claims 17 and 19-21 encompasses on a specific excipient of a polyarginine wherein the independent claims 4, 7, 8, 9 and 17 already has a polyarginine. When only polyarginine is encompassed in claims 19-21, it is unclear when and/or how recited polyarginine in claims 19-21 can be said to be the additional excipient; thus, constitutes as further limiting, in view of newly added limitation of "additional excipient" with or without the recitation of added limitation of "further comprising". For the interest of compact prosecution, claims 19-21 have been interpreted as written, that is including, but not limited to, polyarginine.

Appropriate correction is required.

Withdrawn-Claim Rejections - 35 USC § 112

8. The previous rejection of Claims 9, 17-22, 60-63, 66, 69-72, 74, 77-80 and 82 under of 35 U.S.C. 112, second paragraph, is withdrawn by virtue of applicants' argument. As previously noted, once hGH is administered in any form, it is considered to be bioavailable regardless of for form because it was administered into a body, in view of broad and reasonable interpretation.

Maintained and New-Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 7-10, 17, 19-22, 66-68, and 74-76 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Instant rejection is necessitated by the instant amendment.

Claims 7-9 (Claims 10, 17, 19-22, 63, 66-68, 72-73, 75, 76, and 80 dependent therefrom) recites "wherein the crystal is characterized by...". It is noted that applicants have attempted to make claims with improved format according to the previous objection. The Examiner has suggested the amendment in the previous objection to include the term "complexed" to improve the format of claims such that the scope of claims would not be affected for claims presented at the time of previous claims; and would not necessarily indicate allowability and/or change applicants' scope of interest pursued by the applicants, which is proper. There are two different hGH crystals formulation; that is hGH crystal before polyarginine (recited in the preamble) was added and the other hGH crystal mixed with polyarginine; thus, it is unclear if recited "the crystal" in describing characteristic is referring to hGH crystal complexed with polyarginine. It appear that amending instant claims 7-9 to recite ---wherein the polyarginine complexed with said crystal of hGH is characterized by...---, or ---wherein the hGH crystal complexed with polyarginine is characterized by...---, for example, would overcome instant objection.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 9, 17, 19-22, 63, 68, 72, 76 and 80 are rejected under of 35 U.S.C. 112, first paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Instant rejection is necessitated by the instant amendment.

Claims 9, 17, 19-22, 63, 68, 72, 76 and 80 are rejected under 35 U.S.C. 112, first paragraph, **new matter**, as failing to comply with the written description requirement. The claim(s) contain subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Instant rejection is necessitated by the instant amendment.

Claim 9 (Claims 9, 17, 19-22, 63, 68, 72, 76 and 80 dependent therefrom) recites limitation of "or lower dose". The broad scope of "or lower dose" having any lower dose is not supported by the original disclosure. Applicants argue that support is found at least in tables 6 and 17 of the application (see page 8, lines 6-7, Remarks filed on 2/9/2011). However, the Examiner has reviewed instant Tables 6 and 17; but could not ascertain the scope of claimed product having any lower dose. The applicant is advised to point out the support in the original disclosure or amend the instant claims.

11. Claim(s) 4, 7-10, 17, 19-22, 63-68, 72-76, and 80 are rejected under 35 U.S.C. 112, first paragraph, **written description**, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

The rejection was stated in the previous office action as it applied to previous Claims 4, 7-10, 17-22 and 60-84. In response to this rejection, applicants have amended claims 4, 7-9, 17, 19-21, 63-68, 72-76, and 80; and traverse the rejection as it applies to the newly amended claims.

Applicants argue that instant amendment "to not encompass a co-crystal of polyarginine and hGH" (see page 8, lines 19-20, Remarks filed on 2/9/2011). Applicants also argue "each of the examples is directed to the crystallization of the native hGH, having 191 amino acids, or the native 191 amino acid sequence having an additional N-terminal methionine; thus, in possession of the hGH-polyarginine complexes, as called for by the present claims; wherein the crystallization of hGH are from at least three sources: BresaGen Ltd., Norvatis or Lucky Star (see bottom of page 8 to top of page 9, Remarks filed on 2/9/2011).

Applicants' arguments have been fully considered but are not deemed persuasive for the following reasons. The Examiner acknowledges that there are many native hGHs which are commercially available. However, as previously noted, and in view of instant amendment, instant claims still encompasses a genus of hGH co-crystal comprising hGH, polyarginine polymer and any other additives (in view of comprising);

wherein said hGH is the 191 amino acid sequence of native hGH or with additional Met at the N-terminal residue as well as including, but not limited to, said hGH crystal soaked in polyarginine. The applicants also provided with contradicting argument, that is "applicants tested the ... cocrystals using in vivo animal studies (see Examples 22, 23, 24 and 25)" (emphasis added, see page 9, lines 10-11). It appear that instant Examples 22-25 do show results of *in vivo* testing with hGH consisting 191 amino acid (with or without N-termial Met) soaked in well known excipient of protamine and polyarginine after the crystallization of said hGH; but not the co-crystallized hGH in the presence of polyarginine and/or protamine. The Examiner kindly invites applicants to point out which portion of instant specification discloses the preparation of co-crystallized hGH in the presence of polyarginine and/or protamine.

It is noted that applicants have attempted to make claims with improved format according to the previous objection. The Examiner has suggested the amendment in the previous objection to include the term "complexed" to improve the format of claims such that the scope of claims would not be affected for claims presented at the time of previous claims; and would not necessarily change applicants' scope of interest pursued by the applicants which is proper. Even if, instant claims are interpreted such that it encompasses the hGH crystal soaked in (or mixed with) polyarginine or protamine; as written, in view of instant amendment, it is noted that the characterization followed by recitation of "the crystal" (that is before it was complexed with polyarginine) in claims 7-9 (and all claims dependent therefrom), encompasses that the crystal of said hGH (that is before it was complexed with polyarginine) has the characteristic recited in claims 7-

9; wherein the instant examples only describes the characteristic recited in claims 7-9 are resulted from the function of particular formulation comprising excipient polyarginine or protamine. The applicants and prior art do not describe adequate correlation between structure of claimed hGH crystal consisting of hGH with 191 amino acids (with or without N-terminal Met) with a function described by recited characterizations in instant claims 7-9 and claims dependent therefrom including instant claims 63, 72 and 80. Thus, the applicants failed to convey with reasonable clarity to those skilled in the art that , as of the filing date sought, he or she was in possession of the invention as noted in the breadth of claims in view of broadest and reasonable interpretation of instant claims, according to MPEP §2163.02 as applicants have acknowledged in the middle of page 8, Remarks filed on 2/9/2011. Even if, said hGH is limited to well known native hGH (which consist of 191 native hGH or with additional Met at the N-terminal residue), these disclosed species fail to reflect the variation among the claimed members of the genus, wherein the variation in added agents presented in claimed hGH co-crystallized with polyarginine and optionally with any other agents. See the previous non-final office action, page 8, middle. For all of the reasons above, instant rejection is maintained.

12. Claims 4, 7-10, 17, 19-22, 63-68, 72-76, and 80 are rejected under 35 U.S.C. 112, first paragraph, **scope of enablement**, because the specification, while being enabling for a crystalline human growth hormone (hGH; even if, it is assumed that the amino acid sequence of hGH consist of 191 native hGH or with additional Met at the

N-terminal residue) prepared according to instant Examples 1-4, 6-8 and 10-14 (specification pages 40-51) and soaking or adding with a polyarginine solution (emphasis added), thereby forming a hGH crystal composition comprising hGH:polyarginine; **does not** reasonably enable genus of claimed crystal of hGH:polyarginine with any other agent; or the co-crystallized hGH polypeptide of instant claims in the presence of polyamine; wherein said hGH is the 191 amino acid sequence of native hGH or with additional Met at the N-terminal residue.

The rejection was stated in the previous office action as it applied to previous Claims 4, 7-10, 17-22 and 60-84. In response to this rejection, applicants have amended claims 4, 7-9, 17, 19-21, 63-68, 72-76, and 80; and traverse the rejection as it applies to the newly amended claims.

Applicants argue that the full claim scope is enabled according to the Examiner (see page 10, line 13, Remarks filed on 2/9/2011) and argue that the predictability in the art is directed to general matter whereas the instant claims are directed to crystallization of a few hGH species according to the examples (see page 10, lines 15-19, Remarks filed on 2/9/2011). Applicants argue that instant claims do not allow any variation in the amino acid sequence of hGH how to complex hGH crystals with polyarginine in numerous examples of 1-15 and 18 (see bottom of page 10, Remarks filed on 2/9/2011); thus, applicants argue that one of ordinary skill in the art, would have been able to complex the hGH crystals with polyarginine without undue experimentation.

Applicants' arguments have been fully considered but are not deemed persuasive for the following reasons. However, as previously noted, the full scope of

enablement is not enabled for they require undue experimentation to make and use the full scope of claimed invention. The Examiner is aware of the fact that instant claims are drawn to a native hGH crystal mixed with polyarginine, in view of instant examples), and instant claims, wherein the native hGH has 191 amino acids (with or without N-terminal Met); but just because the polypeptide is limited to a few species of hGH can not overcome issues or difficulties which exist in formation of protein crystal in general; thus, one skilled in the art would not be able to make and use the full scope of instant invention without undue experimentation. As previously noted, the Examiner acknowledges that mixing polyarginine or any other excipient with prepared native hGH crystal can be prepared by one skilled in the art. However, as previously noted, the scope of instant claims includes, but not limited to, any co-crystal of said native hGH in the presence of polyarginine and/or any other excipient in any buffer, and the instant specification failed to provide guidance regarding alterations in the amino acid sequence buffer, for example, as long as said native hGH has 191 amino acids, for example, without requiring any specific amino acid sequence(s); thus, contrary to applicants' argument, instant claims allows any variation(s) in claimed native hGH and polyarginine containing crystal. Thus, without sufficient guidance and direction, the determination of crystallization condition to form claimed genus hGH crystal is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. For all the reasons noted above and previous non-final office action mailed on 08/24/2010, instant rejection is maintained.

Maintained-Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

13. Claims 4, 7-10, 17, 19-22, 63-68 and 72-76 and 80 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sorensen et al. (1998, US Patent 5,849,700 - cited previously) in view of Singh (US Patent 5,788,959, Aug. 4, 1998) and DeFelippis et al. (1998, J. Pharm. Sci., vol. 87, pages 170-176, as cited previously).

The rejection was stated in the previous office action as it applied to previous Claims 4, 7-10, 17-22 and 60-84. In response to this rejection, applicants have amended Claims 4, 7-9, 17, 19-21, 63-68, 72-76, and 80, and have cancelled Claims 1-3, 5-6, 11-16, 18, 23-62, 69-71, 77-79, and 81-84; and traverse the rejection as it applies to the newly amended claims.

It is noted that, in the previous claims, the recitation of "containing crystal of human growth hormone" was in the preamble wherein actual required limitations were polyarginine and hGH (i.e., not hgH crystal) in claims 4, and 7-9; thus, encompassed scope of any mixture of hGH and polyarginine wherein the mixture can be prepared by pharmaceutical formulation as well as co-crystallization set up procedure without actually resulting the co-crystallized product. The instant amendment made it clear that

hGH in claimed composition has to be in a crystalline form. It is also noted that deletion of "wherein the hGH:polyarginine ratio is 12:1 to 3:1 (w/w)" makes claimed scope broader in term of formulation. As noted above, the additional protamine is not necessary in the instant objection since protamine already covers the additional limitation of excipient in claims 17 and 19-22. However, since the limitation of protamine is already examined in view of DeFilippis et al. in the previous office action, to make rejection clearer and make it simpler for any future argument, the disclosure of DeFilippis et al. has been placed in a separate rejection shown below with "in further view of"; thus, it does not a new rejection but continuation of the previous rejection under 35 USC 103(a), but just written in different format.

Relevant arguments by applicants are addressed herein. Applicants argue that Sorensen et al. in view of Singh and DeFelippis et al. do not teach each and every claim limitation because Sorensen disclosing crystallized hGH which comprises with histidine, does not teach or suggest polyarginine complexes of crystallized hGH; thus, "Sorensen does not disclose or suggest polyarginine complexed with a native hGH crystal" (see page 12, lines 5-6, Remarks filed on 2/9/2011); even with US Patent 4,816,568.

Applicants' arguments have been fully considered but are not deemed persuasive for the following reasons. The Examiner notes that, according to MPEP 2144 [R-6], "The rationale to modify or combine the prior art does not have to be expressly stated in the prior art; the rationale may be expressly or impliedly contained in the prior art or it may be reasoned from knowledge generally available to one of ordinary skill in the art, established scientific principles, or legal precedent established

by prior case law. In re Fine, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988); In re Jones, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). See also In re Kotzab, 217 F.3d 1365, 1370, 55 USPQ2d 1313, 1317 (Fed. Cir. 2000) (setting forth test for implicit teachings); In re Eli Lilly & Co., 902 F.2d 943, 14 USPQ2d 1741 (Fed. Cir. 1990) (discussion of reliance on legal precedent); In re Nilssen, 851 F.2d 1401, 1403, 7 USPQ2d 1500, 1502 (Fed. Cir. 1988) (references do not have to explicitly suggest combining teachings); Ex parte Clapp, 227 USPQ 972 (Bd. Pat. App. & Inter. 1985) (examiner must present convincing line of reasoning supporting rejection); and Ex parte Levengood, 28 USPQ2d 1300 (Bd. Pat. App. & Inter. 1993) (reliance on logic and sound scientific reasoning). .... The strongest rationale for combining references is a recognition, expressly or impliedly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent, that some advantage or expected beneficial result would have been produced by their combination. In re Sernaker, 702 F.2d 989, 994-95, 217 USPQ 1, 5-6 (Fed. Cir. 1983). >See also Dystar Textilfarben GmbH & Co. Deutschland KG v. C.H. Patrick, 464 F.3d 1356, 1368, 80 USPQ2d 1641, 1651 (Fed. Cir. 2006) (“Indeed, we have repeatedly held that an implicit motivation to combine exists not only when a suggestion may be gleaned from the prior art as a whole, but when the improvement’ is technology-independent and the combination of references results in a product or process that is more desirable, for example because it is stronger, cheaper, cleaner, faster, lighter, smaller, more durable, or more efficient. Because the desire to enhance commercial opportunities by improving a product or process is universal—and even common-

sensical—we have held that there exists in these situations a motivation to combine prior art references even absent any hint of suggestion in the references themselves.")" (emphasis added). As applicants have recognized (see page 11, bottom, Remarks filed on 2/9/2011), Sorensen et al. explicitly disclose that polyarginine can be added to the hGH crystal in the formulation as a stabilizer; thus, it is the strongest rationale for a *prima facie* case obvious by providing sufficient motivation for one skilled in the art to employ polyarginine with crystallized hGH with a reasonable expectation of success as noted previously (emphasis added).

Applicants argue that according to the Examiner's own argument, the disclosure of polyarginine in a long list of compounds recited by Sorensen to stabilize a non-crystallized form of growth hormone hardily provides one of ordinary skill in the art the motivation to complex polyarginine with an hGH crystal. However, applicants have misunderstanding of the instant rejection under 35 U.S.C. 112, first paragraph which the Examiner have clearly denoted as set forth previous non-final office action mailed out on 8/24/2010 and above in the rejections under 35 U.S.C. 112, first paragraph. The patent by Sorensen et al. explicitly discloses hGH crystal having 191 amino acids; thus, meets all limitation of instant claims which encompasses any 191 amino acids of native hGH and explicitly discloses the use of polyarginine as noted above.

Applicants argue that one of ordinary skill in the art would have at best, used both a positively charged and negatively charged polymer in a non-crystalline hGH complex, otherwise would be in direct contradiction to Singh (see bottom of page 12, Remarks filed on 2/9/2011). Applicants further argue that DeFelippis does not cure the

deficiencies of either Sorensen or Singh as they are silent regarding polyarginine complexed with insuline; thus, no motivation to use protamine as an additional excipient in formulating hGH and polyarginine complex; and concludes the Examiner arbitrarily picking and choosing selected disclosures from Sorensen, Singh and DeFelippis in order to attempt to establish a prima facie case of obviousness instead of any other combination of active agent/polymer/excipient, is a form of hindsight reasoning, which has been condemned by the Supreme court." (see bottom of page 13, Remarks filed on 2/9/2011).

However, in view of Singh is a supporting reference and agents and/or molecule for formulating a pharmaceutical composition with polyarginine or other agents disclosed by Singh is desirable (i.e., more stable and/or more effective, for example) given the general knowledge in the context of art by one skilled in the art. As noted in the previous office action, page 19, lines 2-4 "Contrary to applicants' argument, the addition of polyarginine polymer or protamine as a stabilizer to a protein therapeutic agent is well known at the time of instant invention in view of teachings of Singh and DeFelippis et al. as noted previously (and below); thus, the use of polyarginine and/or protamine is not limited to only insulin in view of Singh and DeFelippis et al. As noted previously (see bottom of page 4 in final office action mailed on 4/13/2009)". Thus, there is no hindsight reasoning in instant rejection in view of disclosure of Singh et al and/or DeFelippis et al. with the rationale to combine the teachings with Sorensen et al. with a reasonable expectation of success. Because polyarginine and/or other agents are specifically taught in the references by Sorensen et al. in view of Singh et al. and

DeFelippis et al. for formulating a useful biological gents, it is noted that the rationale to combine references of the instant rejection does not use impermissible hindsight because it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See In re McLaughlin, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). As noted previously, Sorensen et al. further disclose that "animal growth hormone may be stabilized with various stabilizers to give decreased formation of insolubles and preservation of the soluble activity in aqueous environments" (see bottom of §2); wherein the stabilizer includes "polyarginine" (see §3, line 11). Thus, one skilled in the art would be motivated to add polyarginine and/or protamine into a hGH protein regardless of its form when hGH is to be used as therapeutic agent with a reasonable expectation of success. Also, Singh teach that "preferably about 0.1" and "about 0.5" of polymers weight ratio compared to the therapeutic protein (i.e., 1: 0.1 of protein:polymers, that is equivalent to 10: 1 (or 5:1 using the ratio of said "0.5")); meeting the newly added limitation in claims 4, 7-9 and 81-84. The motivation to do so is that "If the concentration of the two polymers are too high, they may not be injectable", wherein injection is more convenient to utilize (see column 5, lines 10-15). For all of the reasons above instant rejection is maintained.

As noted in previous office actions of the non-final office action mailed on 8/24/2010 (from page 18), final office action mailed on 4/13/2009 (from page 4), and non-final office action mailed on 12/26/2007 (from page 4), Sorensen et al. teach a crystal of human growth hormone (hGH) in the Example 4 (column 13) which consists of the 191 amino acid sequence because “Human growth hormone consists of 191 amino acids" (see column 1, lines 20-21; e.g., a native) as shown in the hGH sequence (see NCBI AAA72260 in the attachment; as cited in the previous non-final office action mailed out on 12/26/2007). The crystal of Sorensen et al. disclose "the polyarginine containing crystal" of hGH reads on a multiple arginine residues in hGH crystal. Sorensen et al. also teach a pharmaceutical composition of said hGH crystal with sodium cation in the Example 9, column 17. Sorensen et al. teach a pharmaceutical formulation comprising a crystal of human growth hormone (hGH, 1.13 mg/ml in §10, line 23) (see Abstract and Example 4 in §13); wherein the “Human growth hormone consists of 191 amino acids" (see column 1, lines 20-21). Sorensen et al. also teach a composition comprising said crystal (1.3 mg/ml) with Benzyl alcohol in Example 7, column 17 (instant Claims 17, 19 and 22). Also, Sorensen et al. disclose that "animal growth hormone may be stabilized with various stabilizers to give decreased formation of insolubles and preservation of the soluble activity in aqueous environments" (see bottom of §2); wherein the stabilizer includes "polyarginine" (see §3, line 11).

Sorensen et al. do not disclose explicitly a composition having a polyarginine as part of the hGH crystal in the examples and do not teach explicitly the limitation of an

additional excipient, e.g., protamine, for example, as encompassed in instant claims 17, 20-21).

Singh teach a drug delivery device comprising "solution of a negatively-charged water-soluble polymer solution and a positively-charged water-soluble polymer" (i.e., a molecule encompassed by the instant recitation of "a cation"; such as polyarginine which has + charge(s) in normal physiological pH) in the presence of a pharmaceutically active ingredient (see Claim 1); wherein the positively-charged water-soluble polymer is polyarginine (see Claim 6) and the pharmaceutically active ingredient is human growth hormone (see Claim 11) which is used for the sustained release of a pharmaceutically active ingredient (see §1, lines 5-6). Singh teach the preferable ratio, by weight, of polymer to pharmaceutically active hGH, for example, "preferably about 0.1" and "about 0.5" of polymer weight ratio compared to the therapeutic protein (i.e., 1: 0.1 of protein:polymers, that is equivalent to 10: 1 (or 5:1 using the ratio of said "0.5")) because if the concentration of the two polymers are too high, they may not be injectable, wherein injection is more convenient to utilize (see column 5, lines 10-15).

DeFelippis et al. disclose the protamine suspension of LysPro (a human insulin analogue) having an “8:1 molar ratio” (equivalent to 1:0.125) of LysPro to protamine (see bottom of left column, page 173 for pharmaceutical preparations of insulin).

Therefore, It would have been obvious to one of ordinary skill in the art at the time the invention was made to make a pharmaceutical composition comprising the hGH crystal of Sorensen et al. by adding polyarginine and/or protamine as a stabilizer and/or as an excipient with a reasonable expectation of success. One would have been

motivated to add a polyamine to the human growth hormone crystal of Sorensen et al. as taught by Singh who teach the polyarginine allows sustained release of a pharmaceutically active ingredient "over a prolonged period of time" (see §2, line 34). The recited crystal characterization of a release profile in Claims 7-9 are inherent characteristics of the pharmaceutical composition comprising the polyamine and the human growth hormone crystal of Sorensen et al. Also, it would have been obvious to one of ordinary skill in the art at the time the invention was made to include hGH of Sorensen et al. with an additional protamine suspension (e.g. 1:0.125 ratio as taught by DeFelippis et al) with reasonable expectation of success because the protamine is the most commonly used intermediate-acting suspension according to DeFelippis et al. (see bottom of left column, page 170). One would have been motivated to include additional protamine into said hGH crystalline suspension since the protamine excipient prolong a pharmaceutical composition in patients and increase the duration of its action (see top of right column, page 170 of DeFelippis et al.) Thus, the invention taken as a whole is *prima facie* obvious for one skilled in the art.

It is noted that Claims 60, 61 and 63 (Claims 69, 70, 72, 77, 78, 80 dependent therefrom) are product by process claims. The factors to be considered for a product-by-process are summarized in MPEP 2113. “[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product

was made by a different process." See In re Thorpe, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985), In re Marosi, 710 F.2d 798, 802, 218 USPQ 289, 292 (Fed. Cir. 1983) and Ex parte Gray, 10 USPQ2d 1922 (Bd. Pat. App. & Inter. 1989). It is also noted the characterization(s) recited in instant claims 7-9 does not contribute a structural limitation of claimed hGH crystal but they are inherent features of hGH when it is in crystalline form as evidenced by the instant specification. Furthermore, according to MPEP 2144.05 [R-5] II, A, "Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955) (Claimed process which was performed at a temperature between 40℃ and 80℃ and an acid concentration between 25% and 70% was held to be prima facie obvious over a reference process which differed from the claims only in that the reference process was performed at a temperature of 100℃ and an acid concentration of 10%.); see also Peterson, 315 F.3d at 1330, 65 USPQ2d at 1382 ("The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages."); In re Hoeschele, 406 F.2d 1403, 160 USPQ 809 (CCPA 1969) (Claimed elastomeric polyurethanes which fell within the broad scope of the references were held to be unpatentable thereover because, among other reasons, there was no evidence of the criticality of the claimed

ranges of molecular weight or molar proportions.). For more recent cases applying this principle, see Merck & Co. Inc. v. Biocraft Laboratories Inc., 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989); In re Kulling, 897 F.2d 1147, 14 USPQ2d 1056 (Fed. Cir. 1990); and In re Geisler, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997).

It is noted that the hGH crystal of Sorensen et al. with added polyarginine would has said characteristics of Claims 7-9 as evidenced by the instant disclosure of pharmacokinetic parameters in applicants' Table 6, in Example 16, page 54-56. Those recited limitations after the "wherein the crystal" clause do not appear to be associated with a particular structure or component of the claimed crystal and have been considered accordingly. Said "limitations" are considered inherent characteristics of the crystal of Sorensen et al. based upon the structure of the crystal. This is evidenced because claimed crystal is of human growth hormone, and based on the rat model as shown in Example 16, the crystal would have the same characteristics when said crystal is administered to a human.

Withdrawn-Double Patenting

14. The previous provisional rejection of Claim 4 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 2, 4, 7, 9 and 10 of copending Application No. 11/169,956 (US 2006/0008532) is withdrawn by virtue of cancelled claims which are drawn to a complex comprising hGH and/or additional agent(s). See claims filed on 9/20/2010.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

15. Claims 4, 7-10, 17, 19-22, 63-68, 72-76, and 80 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 27, and 30 of copending Application No. 12/519,720 Although the conflicting claims are not identical, they are not patentably distinct from each other for reasons set forth herein. Applicant's submission of an information disclosure statement under 37 CFR 1.97(c) with the fee set forth in 37 CFR 1.17(p) on 2/17/2011 prompted the new ground(s) of rejection presented in this Office action.

Claims 1, 27, and 30 of copending Application No. 12/519,720 are drawn to a pharmaceutical composition comprising recombinant hGH (rhGH) with polyarginine

and/or protamine as preferred embodiment, for example, (see specification page ### of copending Application No. 12/519,720); and/or having additional buffers, salts, suspending agents, poly-Arg, preservative and/or hyaluronic acids (see pages 22-29), wherein rhGH includes a recombinantly produced hGH having identical to native rhGH polypeptide sequence (with or without N-terminal Met; see page 16), and wherein the formulation having hGH crystal and polyarginine has inherent characteristics as noted in instant claims 7-9 and claims dependent therefrom. Thus, instant claims are obvious and/or anticipated over the encompassed formulation of claims 1, 27, and 30 of copending Application No. 12/519,720.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

16. Claims 4, 7-10, 17, 19-22, 63-68, 72-76, and 80 are not allowed for the reasons identified in the numbered sections of this Office action. Applicants must respond to the objections/rejections in each of the numbered section in this Office action to be fully responsive in prosecution.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ALEXANDER KIM whose telephone number is (571)272-5266. The examiner can normally be reached on 9AM-5:30PM.
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath Rao can be reached on (571) 272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a

USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Alexander D Kim/
Primary Examiner, Art Unit 1656